Iatrogenic Disorders

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The contemporary physician and his patient are riding the crest of the most dramatic expansion of medical capability in history. But the rapid proliferation of medical knowledge has not been entirely benign. Although our reverses have been minor in contrast to our advances, negative effects cannot be ignored. My discussion involves one aspect of this problem—the emergence of what I have called "Diseases of Medical Progress" (Moser, 1964).

Pertinent to the evolution of medical capability has been the improvement in quantity and quality of drugs. In the early days new drugs came in a trickle, and there was time for the physician to become familiar with their virtues and idiosyncrasies. Soon the trickle became a stream, and there was less time for study and reflection. The stream has now become a torrent; it is impossible for the physician to keep pace. His little black bag runneth over.

It has been said that drug-induced adverse effects are the price we have to pay for more effective medicaments (Zbinden, 1964). There can be no quarrel with this statement; it is the high price we are haggling about. The thalidomide disaster indicated how expensive it can be.

The deluge of new drugs has produced widespread discontent with empiricism in therapeutics. The modern practitioner demands drugs with proper credentials. This has precipitated a virtual renaissance in drug investigation, and thus we have come to learn more of the wonders and hazards of contemporary therapeutic agents.

The demands of the clinician to know more about drugs are being met by increasing capability in the laboratory. New insight and appreciation of the complexities of drug effects have come from several diverse avenues of investigation. The wedding of percutaneous biopsy and electron microscopy has resulted in dramatic revelations; the mysteries of intracellular morphology and physiology in the living organism have begun to yield. Often, we are able to observe the specific site of drug action within the cell.

In other areas techniques continue to be perfected for assay of blood and tissue levels of drugs, intermediate products and enzymes. The problems of adverse drug effects are many. Reduced to simplest elements, when Drug "A" is introduced into the body, ultimately *it* or its intermediate products will be carried in blood and body fluids to all cells of the organism. The effects of Drug "A" become clinically perceptible only when the function of certain organs is modified, either beneficially or detrimentally, to the point of producing perceptible changes, and it is by these phenomena that we learn to characterize the nature of Drug "A." As we focus attention upon the response of a specific organ (or organs) to this drug, we are inclined to *forget* that Drug "A" is also in contact with other tissues of the organism. Effects in

these areas are not immediately detectible, but may become manifest clinically at a later date. Such long-range effects may never be correlated with the antecedent administration of Drug "A."

Only painstaking retrospective analysis of many cases will uncover a suspected denominator. Then we must follow with a meticulously controlled prospective study which will involve provocative testing in acceptable laboratory animals before we can prove that indeed it was Drug "A" that caused the chronic disease. The problems of extrapolating this data to humans are evident. This is a shadow world of pathophysiology where relation of cause to effect is at best difficult to assess. I need only cite the still raging controversy over phenacetin and renal disease to demonstrate the difficulty. There are other problems.

What is known of the role played by drugs in predisposing the organism to attack by micro-organisms or degenerative disease? An example is the effect of long-term corticosteroids in predisposing the leukemia or lymphoma patient to systemic fungus infections.

We are hearing more about the so-called "opportunistic organisms" —perhaps a semantically poor euphemism. But it is appropriate to our thesis to mention *Candida albicans* (Seelig, 1966). This is a saprophyte of limited pathogenicity under normal circumstances, but may emerge as a systemic infection and seed into many organs during or following broad spectrum antibiotic administration, with or without concomitant corticosteroid or immunosuppressive therapy. This phenomenon has been related to suppression of susceptible enteric flora with disruption of the normal ecologic balance permitting the unsuppressed saprophytes to proliferate and escape their enteric confines.

The devastating influence of prolonged corticosteroid therapy upon the elderly patient immobilized by cardiovascular disease or arthritis, in whom accelerated demineralization occurs through corticosteroid anti-anabolic effect, is an example of exaggeration of degenerative disease caused by a drug. We start with one disease and our treatment for it produces another disease.

Let us modify the question again. What is known of the effects of drugs upon a previously diseased organ, with limited capability to metabolize or detoxify or otherwise cope with a drug given to treat another illness? I have mentioned the phenacetin controversy. The discussion here revolves around the status of analgesic compounds in the provocation of interstitial pyelonephritis in a normal kidney. But what effect do phenacetin, aspirin, or the combination have upon a sick kidney, already poorly disposed to resist assault from either micro-organism or nephrotoxic drug?

Consider the patient with subclinical hepatic disease, e.g., a mild cirrhosis, who is given chlorpromazine or phenylbutazone, drugs known to be occasionally toxic to the liver. One could cite multiple examples wherein an organ with marginal function may be further insulted by a drug administered, most innocently and with proper indication, to treat another ailing system.

Pharmacogenetics and Enzyme Induction

Perhaps the most fascinating corollary to these observations is the identification of a relationship between enzyme systems and drug effects. Vogel (1959) introduced the term "pharmacogenetics" into clinical medicine. This was defined as "the study of genetically determined variations that are revealed *solely* by the effects of drugs." The genetic variation results in the absence or insufficiency of certain enzyme systems. This mechanism has already been cited as one major explanation of the extraordinary human variability in response to conventional doses of conventional drugs (Evans, 1963).

The historical and classical example of a pharmacogenetic disease is the hemolytic anemia suffered by some members of certain ethnic groups, specifically, Mediterranean basin dwellers and Negroes (Berry, 1965; Beutler et al., 1955). Brisk hemolysis may follow exposure to many common therapeutic agents (among these are the 4-aminoquinolines, certain sulfonamides, acetylsalicylic acid, the nitrofurantoins, sulfones, para-amino-salycylic acid, phenacetin acetanilid, probanthine and the water soluble analogues of vitamin K). Even the Fava bean apparently provokes hemolytic anemia on the same basis.

The cause is a genetically transmitted defect that results in deficiency of the intra-erythrocytic enzyme, glucose-6-phosphate dehydrogenase. Such patients are normal clinically; they have no morphologic or physiologic abnormality of their red cells, until one of the provocative drugs is given. Then brisk hemolysis occurs. Deficiency of glucose-6-PD has been cited as one cause of neonatal jaundice. It is somewhat of a problem in the chloroquine primaquine anti-malarial prophylaxis program in Southeast Asia (personal communication, Col. Marshal McCabe).

Other red cell enzyme deficiencies of greater subtlety have begun to emerge; these include aldolase, catalase, glutathione, glutathione reductase, pyruvate kinase, triose phosphatase and isomerases.

In addition, kernicterus of the newborn is related to immaturity of the neonatal liver. This organ is deficient in glucoronosyl transferase and, therefore, unable to conjugate bilirubin. Administration of sulfisoxazole (Gantrisin) or vitamin K analogues exaggerates this reaction. Novobiocin may provoke jaundice in the newborn and rarely in adults by direct inhibition of glucoronosyl transferase (Moser, 1967, in press).

Do these adults have a marginal

deficiency of this enzyme which becomes evident only when they are challenged with novobiocin? Is it congenital, or is it acquired as the result of a preceding episode of hepatic disease?

There are other equally fascinating pharmacogenetic diseases. Hemoglobin Zurich (Frick, Hitzig, and Betke, 1962) is an example. If a certain Swiss family had not been given sulfonamide drugs, it is quite likely that this abnormal hemoglobin disease would have continued to escape detection. A frank hemolytic anemia developed after administration of sulfadimethoxine and sulfamethoxypyridizine (Kynex) to family members. A new hemoglobin with electrophoretic mobility between A and S was identified; fingerprints of peptic digests revealed three unusual peptides.

Time permits only a brief glance at other equally fascinating pharmacogenetic disorders.

(1) Hemoglobin H disease: patients with this illness have hemoglobin which is a tetramer of four beta chains. Their erythrocytes appear normal until they are given sulfisoxazole; then a brisk hemolytic anemia may develop.

(2) Patients may be divided into phenotypes on the basis of their ability in inactive isoniazid (Porter, 1964; Editorial, S. African Med. J., 1964). There is reason to suspect that isoniazid polyneuropathy is more common in "slow inactivators" than "rapid inactivators." Fortunately there is no difference in therapeutic responsiveness to isoniazid, and the development of resistance by the tubercle bacillus to isoniazid is similar in the two phenotypes.

(3) About 1% to 2% of patients have a genetically determined deficiency of pseudocholinesterase (Hodgkin et al., 1965); This may be qualitative or quantitative. The malady will remain asymptomatic and undetected unless the patient is challenged with suxamethonium. Then the response is dramatic; a 2 to 3 min period of apnea will ensue. Pseudocholinesterase is required to metabolize suxamethonium.

(4) It is suspected that increased susceptibility to dyskinesias subsequent to administration of phenothiazines such as chlorpromazine, may have a genetic basis.

And in view of the multitude of known enzyme systems, as well as those suspected but not as yet identified, one could predict that many reactions now classified as idiosyncratic or hypersensitive will soon be gathered into the fold of pharmacogenetic disorders or acquired enzyme insufficiencies.

A related phenomenon is drug-induced inhibition of the metabolic breakdown or release of albumin binding with escape of free drug. This is epitomized by the potentiation of coumarin drugs by several rather common agents, such as phenyramidol (Carter, 1965), acetyl salicylic acid, tetracycline, streptomycin, D-thyroxine, androsteneolone, phenylbutazone (Eisen, 1964) and oxyphenbutazone (Fox, 1964).

Now there is a new dimension, quite antithetical to the concept of enzyme deficiencies unmasked or inhibition of metabolic breakdown caused by drugs. This is the phenomenon of "enzyme induction," in which the administration of one drug accelerates the metabolic breakdown of another. (Burns, et al., 1965; Conney and Burns, 1963; Fouts, 1963). Clinical suspicion was aroused when it was discovered that some patients receiving coumarin drugs required increased doses to maintain therapeutic anticoagulant levels while taking barbiturates.

Residual Drug Effects

Residual drug effects remain another enigmatic area. For example, reserpine continues to exert its influence in certain patients for several weeks after it has been discontinued. It may cause unpredictable responses to general anesthesia. Reserpine may obscure the phentolamine (Regitine) test for pheochromocytoma for several weeks after it has been stopped. The persisting and even progressive retinal damage induced by residual chloroquine has been the subject of much commentary.

Elevated levels of protein bound iodine were found in the sera of women who had received iophenoxic acid (Teridax, a cholecystographic medium) six to seven years previously. Babies born several years after their mothers had ingested iophenoxic acid had extremely high levels of protein bound iodine (Goss and Dickhaus, 1965). These agents may lie dormant in fat depots for many years, apparently innocuous, but in curious contradiction to the usual tendency of an organism to rid itself of foreign substances. What other drugs are "stored" for prolonged periods? Do they exert adverse effects? Questions come easily; answers do not.

An equally fascinating new aspect of drug mechanisms is revealed in the recently recognized phenomenon of transferable drug resistance. This was first observed in Japan in 1959 during studies on *Shigella* which proved resistant to several anti-microbial agents. It is now recognized that *Shigella* and *Salmonella* are capable of genetic transmission of drug resistance (Smith, 1966). It has been suggested that the widespread use of antibacterial drugs in agricultural feeds has contributed to this problem. To my knowledge genetically transferred resistance factors have been identified only in gram-negative micro-organisms and acid-fast bacilli.

Now that we have seen something of the broad introductory area of drug-induced diseases, a logical question might be: What will be the ultimate effect of these new therapeutic endeavors? The answer must lie somewhere in the interface between philosophy and physiology.

The evolution of man is a continuing source of wonderment to students of physiology. Through the centuries of painful metamorphosis, each challenge thrown at man by his environment was met by a gradual genetic modulation that enabled him to survive. The species has arrived at the current state of advanced physiologic capability—admirably adapted to its environment. We can dig diamonds at 9,000 feet in 123° heat and 100% humidity; we can spend a lifetime mining tin at a 14,900-foot elevation, we can hike across the pole, and we can float weightless-in-space for 14 days.

But in the past few decades we have devised techniques unprecedented in the previous experience of the species to challenge the adaptability of the organism. We have designed molecules unique to human physiology and have intruded them into blood and tissue by techniques that are also unique in physiologic experience. Intravenous, intramuscular and subcutaneous injections, positive pressure inhalation, rectal administration, and agents that facilitate passage through intact skin all are unfamiliar modes of gaining access to the body. Add, for example, radiation by x-ray, beta ray, gamma ray and neutrons, plus oxygen under greatly increased barometric pressure, and one begins to appreciate the magnitude and genius of man's conspiracy to by-pass the conventional avenues for introducing new environmental factors to the physiology of man.

In the past we only had to cope with nature and environment. And they were confined to the gastrointestinal tract, lungs and occasionally the abraided skin to admit alien materials to the core of man.

The implications of these ingenious tactics of assault, these strange man-made chemicals and emanations upon the beleaguered human mechanism are fascinating to contemplate. One could speculate that this incredibly resilient physiologic machine of ours is sufficiently advanced in design to be able to cope with all transgressors. We have evolved defenses at all levels from the simplest reflex to the most complex immune reactions to meet the daily challenges of environment. And we have done very well in the matter of self preservation.

Yet it is quite evident that some of these unprecedented therapeutic intrusions will overtax the ability of the body to accommodate, and it will react with displeasure, if not violent rejection. Of course this is the heart of our thesis, drug-induced diseases.

Every new drug must be evaluated for efficacy and toxicity, and this is not an easy task. Only passage of time and acquisition of experience will determine the ultimate verdict. Firm pronouncements based on animal experimentation or fragmentary early clinical trials are premature and meaningless. Often it takes years before the full spectrum of efficacy or toxicity of a drug becomes evident. This poses an almost insoluble conundrum. If we are timid and withhold the drug, how will we ever gain the necessary clinical experience? If the agent is effective and safe, it would seem unfair to withhold it. But if the drug is ineffective or toxic, it would seem equally unfair to use it on patients. All that one can propose is prudence, caution, and reservation of final judgment until objective studies are completed.

In an effort to dramatize the problem of drug toxicity, I have selected one group of drugs, the tetracyclines, to serve as a prototype to illustrate the continuing challenge that faces the medical profession in arriving at a comprehensive appreciation of the spectrum of toxic effects of drugs. One might select almost any popular drug to do the same thing. This could properly be called the evolution of the toxic profile of a drug.

Tetracyclines are valuable therapeutic allies. They qualify as antibiotics of choice in a host of in-

fectious diseases. So let it be established at the outset, there is no denying the efficacy of tetracyclines in clinical medicine.

Included in this group of drugs are chlortetracycline (Aureomycin) oxytetracycline (Terramycin), tetracycline, tetracycline phosphate and rolitetracycline.

Chlortetracycline was introduced in 1947. Despite the wearisome flurry of superlatives that attends the introduction of every major new drug, chlortetracycline was found to be remarkably effective. By 1949, a reflective review of the literature on this drug stated "it is an important landmark in the field of antibiotics. Its extremely low toxicity and wide range of activity and absorbability from the gastrointestinal tract combine to make it a powerful therapeutic weapon" (Rose and Kneeland, 1949). A prodigious literature extolling its virtues soon accumulated.

Early adverse effects were minor. They could almost be characterized as annoyances, and they were confined to the gastrointestinal tract. Loss of appetite, nausea, vomiting, flatulence, dyspepsia and diarrhea occurred in about 10% of patients receiving significant doses (Pflug, 1963; Schindel, 1965; Bevelander, 1963). For several years the profession was quietly congratulating itself on having found a new variety of wonder drug with broad application and low toxicity. Even the appellation "broad spectrum antibiotic" had a solid ring, adding a dimension of comprehensive coverage and confidence.

In the early 1950's slight rumblings could be heard in this therapeutic paradise. Other adverse effects related to gastrointestinal tract, more severe than the early ones, began to creep into clinical cognizance.

Antibiotics, especially the tetracyclines, can disrupt the normal ecologic balance of the colon. Destruction of friendly commensals facilitates overgrowth of organisms resistant to the antibiotic. And, of course, if any of these hostile bacteria escape their enteric confines and gain access to blood or urinary tract, they can cause significant mischief.

This alteration of bacterial flora has been associated with stomatitis, glossitis, pharyngitis, and black hairy tongue, a cosmetically grotesque, but pathologically benign condition. Also xerostomia, hoarseness, and vulvo-vaginitis were related to tetracycline treatment. In most of these situations, disruption of bacterial balance permitted the fungus *Monilia Albicans* to flourish in these unseemly sites (Pflug, 1963; Bonniot, 1964; Caruso, 1961; Clendenning, 1965).

A corollary phenomenon was the rare occurrence of bleeding in elderly patients with cirrhosis of the liver. It was postulated that the damaged liver was less efficient in producing its coagulation factors. Added to this was the belief that Vitamin K synthesis in the small bowel was inhibited by the alteration of flora incident to tetracycline administration. But now this mechanism is strongly disputed. A final step in this hypothetical pathogenesis was that the sick liver, already struggling to produce its coagulation factors, had its supply of Vitamin K cut off. Therefore, no Vitamin K, no coagulation factor—and we have bleeding. Unfortunately, there is little evidence to support this concept.

It was in 1958 that from the British Isles, Germany, and Scandanavia came word that an old scourge was revisiting us with a vengeance. This was the granddaddy of all gastrointestinal syndromes that tetracyclines and other antibiotics had caused: staphylococcal pseudomembranous entercolitis (Bonniot, 1964; Caruso, 1961; Clendenning, 1965; Altemeier, Hummel, and Hill, 1963; Nemeth, Feher, and Szinay, 1963; Pockrandt, 1964; Sivertssen and Juel, 1958; Wegmann and Bucher, 1964). Once the friendly bacteria had been decimated by the antibiotic, the *Staphylococcus,* previously suppressed by normal bacterial inhabitants, had gained ascendency and invaded the colon wall. This resulted in destruction of the superficial cellular layers, with necrosis and sloughing. The result was a denuded colon wall which wept vast amounts of fluid, and death was not an infrequent consequence.

This dread complication had been known before antibiotics, but there was a distinct impression that the incidence had risen significantly with the use of antibiotics, including the tetracyclines. It was a tragic paradox that in some instances the antibiotics had been given in a sincere but naive effort to prevent the development of a bacterial infection.

In the early 1960's, rare sporadic cases were recorded describing a variety of hypersensitivity reactions. These included sudden cardiovascular collapse due to anaphylaxis, (Bedford, 1951; Editorial, *J.A.M.A.*, 1965; Fellner and Baer, 1965). Others included ecchymoses (Schoenfeld, 1964), hemolytic anemia (Takahashi, 1963), and dermatologic reactions (Schindel, 1965).

A related and even more curious problem was the reactivation of systematic lupus erythematosus (Domz et al., 1959). Some observers even reported the precipitation of this disease de novo, following the administration of tetracyclines (Sulkowski and Haserick, 1964). This must be an unusual occurrence, since I have seen no subsequent reports.

In early 1963, a paper appeared which described a new entity related to tetracyclines. It bore superficial resemblance to diabetes mellitus, since there was an excess of glucose in the urine and even albumin. But closer scrutiny revealed that amino-acids also were being excreted. Thus it conformed to the pattern that had only been observed previously in patients with the Fanconi syndrome (Cleveland et al., 1965; Castell and Sparks, 1965;

Editorial, *Medicina,* 1965; Frimpter, Timpanelli; and Eisenmenger, 1963; Fulop and Drapkin, 1965; Gross, 1963; Rice, Anderson, and Clark, 1964).

It was an intriguing situation, especially when the cases were collated and it was discovered that all victims had ingested out-dated tetracycline. The mysterious malady regressed about one month after the drug had been withdrawn.

Warnings went out to physicians and pharmacists advising them to prescribe precise amounts of tetracycline and to admonish thrifty patients to clean out the medicine chest. The American tradition of family sharing of unused antibiotics was publicly denounced.

A paucity of subsequent reports seemed to indicate that the pharmaceutical industry had modified the procedure by deleting citrate to obviate the problem of tetracycline degradation. However, two recent cases were reported in which potassium depletion was a remarkable feature of a Fanconi Syndrome, again induced by out-dated tetracycline.

This incident called to mind some earlier work linking tetracycline toxicity and renal disease (Editorial, *Ann. Int. Med.*, 1963; Mavromatis, 1965; Pulliam and O'Leary, 1964; Robins, 1963; Shils, 1963; Solomon, Galloway, and Patterson, 1965; Wegienka and Weller, 1964; Zimmerman and Werther, 1964). These antibiotics tend to interfere with protein synthesis. In patients with poor kidney function, tetracyclines may exaggerate elevation of blood urea nitrogen. Rarely, an excessive sodium diuresis may cause hyponatremia. As the kidney disease becomes more severe and function declines, the tetracycline-induced problems are compounded proportionately. Severe retention of protein breakdown products, urea and phosphate, result in a metabolic acidosis, and this could cause loss of weight, uremic symptoms, including anorexia, nausea and vomiting. Tetracycline adminstration to the unfortunate patient with severe renal disease may result in exacerbation of clinical uremia; gastric ulceration and bleeding has been reported.

In 1963 a new dimension was added to the tetracycline story. It was discovered that these drugs had a strange affinity for teeth, bones and tumors (Benson, 1964; Cuttita, 1965; Editorial, *J. Am. Dental Assoc.*, 1964; Editorial, *Lancet*, 1965; Editorial, *Nutrition Rev.*, 1964; Frankel and Hawes, 1964; Hilton, 1962; Kutscher, et al., 1963; Kvaal, 1965; Madison, 1963; Stewart, 1964; Swallow, 1964; Taguchi, 1963; Vickers, 1964; Wallman and Hilton, 1962; Weyman, 1965; Witkop and Wolf, 1963). A group of 50 young children were receiving long-term chlortetracycline or oxytetracycline for the control of pulmonary infection associated with cystic fibrosis. Staining of the teeth occurred in 80%. Those given tetracyclines in early infancy exhibited the most severe discolorations.

Apparently tetracycline has an affinity for the active growth sites of bones and teeth; it migrates to these areas soon after it is given, and there it remains. A definite inhibition of normal calcification occurs at these sites of tetracycline deposition.

In teeth this amounts to delayed growth and intrinsic staining of dental enamel; this may be the commonest cause of deciduous enamel discoloration in infants.

Perhaps equally distressing is the capability of tetracyclines to migrate through the maternal placenta to be deposited in the skeleton of the fetus (Tubaro, 1964). In premature infants this could cause inhibition of bone growth. On a happier note, it must be noted that this effect is reversible if the course of tetracyclines given to the mother is brief.

Other authors have suggested that tetracyclines administered to women in early pregnancy could result in congenital abnormalities in their off-spring (Barkalaia, 1964; Manning, 1964; Cohlan, Bevelander, and Tiamsic, 1963). The data here was entirely inferential. This did call to mind a paper published in 1963, which described a strange phenomenon in which tetracyclines administered to six infants caused a rise in cerebro-spinal fluid pressure with bulging of the fontanelle. This process regressed promptly upon withdrawal of the drug (Opfer, 1963). This is most assuredly a rare adverse effect. I have seen no subsequent reports of this phenomenon.

In another direction it has been observed that some individuals who are taking tetracyclines develop increased sensitivity to sunlight (deVeber, 1962; Kingsley, 1963; Saslow, 1961; Sogal, 1963; Storck, 1965; Tromovich and Jacobs, 1963). This apparently is more severe with demethylchlortetracycline, but has occurred with others of the group. This may take a rather severe form on rare occasions with actual epidermolysis.

Later a report described a young lady who became myopic while taking tetracycline; it disappeared when she stopped the drug (Capperucci, 1964; Edwards, 1963). Later a few others made similar observations.

In 1964, Dr. Searcy and coworkers reported that tetracycline when given intravenously interfered with coagulation of blood (Searcy, Simms, and Foremar, 1964; Searcy et al., 1965). This was considered to be a direct effect against specific clotting factors. These patients did not have liver disease and there was no apparent disturbance of Vitamin K production.

In late 1963, the *New England Journal of Medicine* carried an article that described the deadly misfortunes of six young pregnant women who developed kidney infections. They were given tetracycline intravenously in larger than average doses by the intravenous route. All died within 5 to 13 days after the start of tetracycline treat-

ment. Examination at post mortem revealed identical changes in their livers (Schultz et al., 1963). Several more cases were reported subsequently (Brewer, 1965; Cairella, Trasatti, and Becchi, 1964; Editorial, *Brit. Med. J.*, 1964; Finn and Horwitz, 1965; Horwitz and Marymont, 1964; Kunelis, Peters, and Edmondson, 1965; Norman, Schultz, and Hoke, 1964; Orentreich and Berger, 1965; Popper et al., 1965: Wruble et al., 1965; Wruble and Cummins, 1965).

This episode was climaxed by a formal statement by the American Medical Association, Council on Drugs. "Tetracycline given intravenously should be prescribed with caution in women in the last trimester of pregnancy. When administered, its concentration in serum should be controlled and liver function tests should be made at frequent intervals. Finally, it is important that physicians refrain from prescribing other potentially hepatotoxic drugs concomitantly" (Dowling and Lepper, 1964).

This appeared on April 20, 1964. It was a conservative statement at the time. Today we have other drugs with the same area of effectiveness as tetracyclines, but with no known toxic effect upon the liver.

And all of this is not over. Just a few months ago an article appeared describing thrombocytopenia related to tetracyclines (FDA Reports, 1966). And this was almost 20 years after the first clinical experience with this group of drugs.

Again I wish to emphasize that tetracyclines are valuable antibiotics. I prescribe them; all of us do, but they are not entirely benign (Moser, 1966). And it has taken almost 20 years to appreciate this.

One may ask, how can it be that it takes so long? The answer is not easy. I can cite my own experience with another drug. Soon after it appeared on the market, I prescribed Serpasil for a patient. Soon she complained of paresthesias and tremors.

I searched the literature; there was nothing. I considered this a neurotic manifestation, patted my patient on the head, and persisted in my naivete and ignorance. Finally symptoms became more severe; I stopped the drug; symptoms regressed. I started the drug again; symptoms recurred. At least I was convinced. The patient (who happened to be my wife) was also convinced that I was an idiot. And one week later the first article appeared on Serpasil-induced tremors. This is not an uncommon experience, and that is why it often takes 20 years.

Conclusion

"Diseases of Medical Progress" will be with us forevermore. They cannot be swept under the rug, either by clinician or drug producer. My own naivete in the world of commerical enterprise is revealed by my admission that I think a fine new drug will become known to the profession on the basis of its merit. I am embarrassed when this noble community is demeaned by merchandizing techniques, however subtle or artful, better suited to less vital products, such as soap or soda pop. The fact that over $750 million is spent each year for drug advertising is a staggering testimonial to the enormity of this effort. This is almost three times more money than is required to run all of the medical schools in this country for one year. I do not feel that drugs should be propagandized to the medical profession. The pressure of commercial competition is not conducive to objectivity in the presentations of drug detail men or in published advertisements. I feel these factors add to the confusion in the already difficult problems of evaluating the efficacy or adverse effects of new drugs.

The requirement for an impartial agency that can provide current, reliable and objective data about the characteristics of new drugs, and alert the physician to their toxic hazards is abundantly evident. This requirement has been met by the American Medical Association Council on Drugs, which created a national "Registry of Adverse Reactions." A comparatively new facility, it was the natural successor to the "Registry of Drug-Induced Blood Dyscrasias," a most successful pioneer study guided and nurtured by Dr. Maxwell M. Wintrobe and Dr. Charles Huguley. The new, broader registry makes it possible for any physician to contribute his personal experience with adverse drug effects to a central pool. This information is recorded on a form designed for automatic data processing. The data are extracted and recorded in the memory banks of a computer system.

Volunteer teams of nationally recognized specialists study all information submitted to the Registry. Thus, the input from physicians throughout the country is evaluated and recorded. Hopefully, for the first time, we have the means to obtain realistic incidence data about adverse drug effects. The response from hospitals and private physicians has been disappointing, in quantity and quality but the program is young, and already the Journal of the American Medical Association has carried several brief pertinent articles describing recently discovered adverse drug effects and summarizing drug information derived from this new facility.

The Federal Drug Administration has inaugurated a similar program that complements the AMA Registry and expands the total data gathering capability. FDA concern in the matter is oriented somewhat differently from that of the AMA. Nevertheless, such activity in the nation's highest medical councils indicates the growing importance of adverse drug effects.

The AMA Registry represented a significant step toward meeting the challenge of new responsibility that accompanies increased capability. Our remarkable therapeutic arsenal

is a tribute to the commercial drug industry and the devoted chemists and pharmacologists of our medical schools. But neither medical schools, AMA, FDA, nor the industry can solve the problem completely.

My plea has been, and is directed to the physician on the firing line, the doctor who prescribes the drug. It is farthest from my intention to suggest therapeutic timidity or homeopathy. Our predecessors in medicine had limited diagnostic and therapeutic resources. The complement of nostrums in their little black bag was austere, but these drugs were regarded as old familiar friends. Some were worthless, others dangerous; some were impure and unstandardized to the point of unpredictability. The few effective drugs were trusted allies whose strengths and weaknesses were well known. The practitioner of the past attempted to compensate for lack of material resources with meticulous attention to his patients, personal charm, kindness, and pervading equanimity.

His lonely hours of private hell, tormented by his inability to come to grips with most of the severe illnesses that he encountered, constitute a long, bleak chapter in medical history. The modern physician is afforded rare glimpses of this agony when faced with malignancy or degenerative disease or neurologic illness. Modern pharmacology has brought this unhappy era to an end; we now enjoy the privilege of fine, powerful, well-standardized therapeutic weapons.

Now we must work to create an atmosphere of rational caution and critical evaluation, where each physician will pause before putting pen to prescription pad and ask himself, "Do I know enough about this drug to prescribe it? Does the possible benefit I hope to derive from this drug outweigh its potential hazard?" I do not preach therapeutic nihilism, but rather *therapeutic rationalism.*

Thank you.

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